

EXHIBIT 46

**DEPARTMENT OF HEALTH AND HUMAN SERVICES
CENTERS FOR DISEASE CONTROL AND PREVENTION
National Center for Emerging and Zoonotic Infectious Diseases
Division of Healthcare Quality Promotion**



Healthcare Infection Control Practices Advisory Committee
March 31, 2016
Atlanta, Georgia

Record of the Proceedings

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Meeting Agenda

Healthcare Infection Control Practices Advisory Committee

March 31, 2016

Centers for Disease Control and Prevention

Tom Harkin Global Communications Center (Building 19, Auditorium 3)

1600 Clifton Road NE, Atlanta, GA

Thursday, March 31, 2016

Time	Topic	Purpose	Presider/Presenter
9:00	Welcome and Introductions	Information	Dan Diekema (HICPAC Co-Chair) Deborah Yokoe (HICPAC Co-Chair) Jeff Hageman (HICPAC DFO)
9:15	CDC Updates: Division of Healthcare Quality Promotion (DHQP)	Information	Denise Cardo (DHQP, CDC)
9:45	FDA Device Updates: Flexible Endoscopes and Heater Coolers	Information Discussion	Suzanne Schwartz (FDA) Catherine Wentz (FDA)
10:35	Break		
10:55	Update on HICPAC Workgroup: Endoscope Reprocessing	Information Discussion	Lisa Maragakis (HICPAC)
11:45	Device Considerations	Information Discussion	Michael Bell (DHQP, CDC) Shannon Keckler (DHQP, CDC)
12:30	Lunch		
1:45	FDA PPE Update: Gowns	Information	Terrell Cunningham (FDA)
2:00	Update on HICPAC Workgroup: Antimicrobial Stewardship Principles for Treatment Guidelines	Information Discussion	Jan Patterson (HICPAC)
2:50	Chlorhexidine-Impregnated Dressing Recommendation Update	Information Discussion	Erin Stone (DHQP, CDC) Tom Talbot (HICPAC)
3:40	Break		
4:00	Update on the Draft Guideline for Infection Prevention in Healthcare Personnel	Information Discussion	David Kuhar (DHQP, CDC) Katy Irwin (DHQP, CDC)
5:00	Public Comment		
5:15	Liaison/ <i>ex officio</i> reports		
5:30	Summary and Work Plan		
6:00	Adjourn		

List of Participants

March 31, 2016

HICPAC Members

Dr. Daniel Diekema, Co-Chair
 Dr. Deborah Yokoe, Co-Chair
 Dr. Hilary Babcock
 Ms. Vickie Brown
 Ms. Loretta Fauerbach
 Dr. Michael Howell
 Dr. W. Charles Huskins
 Ms. Lynn Janssen
 Dr. Lisa Maragakis
 Dr. Jan Patterson
 Dr. Tom Talbot

Ex Officio Members

Ms. Elizabeth Claverie-Williams, Food and Drug Administration
 Dr. David Henderson, National Institutes of Health
 Dr. Melissa Miller, Agency for Healthcare Research and Quality
 Dr. Gary Roselle, Veteran's Administration
 Dr. Daniel Schwartz, Centers for Medicare and Medicaid Services
 Ms. Judy Trawick, Health Resources and Service Administration

Liaison Representatives

Mr. Michael McElroy (America's Essential Hospitals (AEH))
 Dr. Elizabeth Wick (American College of Surgeons (ACS))
 Ms. Amber Wood (Association of periOperative Registered Nurses (AORN))
 Ms. Michael Anne Preas (Association of Professionals of Infection Control and Epidemiology (APIC))
 Dr. Emily Lutterloh (Association of State and Territorial Health Officials (ASTHO))
 Ms. Marion Kainer (Council of State and Territorial Epidemiologists (CSTE))
 Dr. Stephen Weber (Infectious Diseases Society of America (IDSA))
 Dr. Sarah Matthews (National Association of County and City Health Officials (NACCHO))
 Ms. Laurie O'Neil (Public Health Agency of Canada (PHAC))
 Dr. Craig Coopersmith (Society for Critical Care Medicine (SCCM))
 Dr. Mark Rupp (Society for Healthcare Epidemiology of America (SHEA))

Dr. Vineet Chopra (Society of Hospital Medicine (SHM))
 Dr. Robert Sawyer (Surgical Infection Society (SIS))
 Ms. Margaret VanAmringe (The Joint Commission)

FDA Representatives

Mr. Terrell Cunningham, FDA/ CDRH
 Dr. Catherine Gaylord, FDA
 Ms. Julia Marders, FDA/ CDRH
 Ms. Elaine Mayhall, FDA/ CDRH
 Dr. Kapil Panguluri, FDA/ CDRH
 Dr. Suzanne Schwartz, FDA/ CDRM

CDC Representatives

Ms. Jessica Adam, CDC/ DHQP
 Ms. Denise Albina, CDC/ DHQP
 Ms. Kathy Allen-Bridson, CDC/ DHQP
 Dr. Matt Arduino, CDC/ DHQP
 Ms. Sonya Arundar, CDC/ DHQP
 Dr. Michael Bell, CDC/ DHQP
 Ms. Ruth Bellflower, CDC/ DHQP
 Ms. Kathy Bruss, CDC/ DHQP
 Ms. Katy Capers, CDC/ DHQP
 Dr. Denise Cardo, CDC/ DHQP
 Dr. Matthew Crist, CDC/ DHQP
 Dr. Bryan Christiansen, CDC/ DHQP
 Ms. Nicoline Collins, CDC/ DHQP
 Ms. Katelyn Coutts, CDC/ DHQP
 Ms. Mahnaz Dasti, CDC/ DHQP
 Dr. Chad Dowell, CDC/ NIOSH
 Dr. Ryan Fagan, CDC/ DHQP
 Dr. Scott Fridkin, CDC/ DHQP
 Ms. Nancy Gallagher, CDC/ DHQP
 Ms. Janet Glowicz, CDC/ DHQP
 Dr. Carolyn Gould, CDC/ DHQP
 Ms. Pam Greene, CDC/ DHQP
 Dr. Nicole Gualandi, CDC/ DHQP
 Mr. Taylor Guffey, CDC/ DHQP
 Ms. Stephanie Gumbis, CDC/ DHQP
 Mr. Jeff Hageman, CDC/ DHQP
 Dr. Lauri Hicks, CDC/ DHQP
 Dr. Kathleen Irwin, CDC/ DHQP
 Mr. Brendan Jackson, CDC/ NCEZID/ DFWED/ MDB
 Dr. John Jernigan, CDC/ DHQP
 Dr. Mary Shannon Keckler, CDC/ DHQP
 Dr. David Kuhar, CDC/ DHQP
 Dr. Jason Lake, CDC/ DHQP
 Dr. Brandi Limbago, CDC/ DHQP
 Dr. Meghan Lyman, CDC/ DHQP
 Dr. Cliff MacDonald, CDC/ DHQP

Dr. Rajal Mody, CDC/ NCEZID/ DFWED/ MDB
 Ms. Shunte Moon, CDC/ DHQP
 Ms. Kerri Moran, CDC/ DHQP
 Ms. Heather Moulton-Meissner, CDC/ DHQP
 Dr. Duc Nguyen, CDC/ DHQP
 Dr. Judith Noble-Wang, CDC/ DHQP
 Ms. Amibola Ogundimu, CDC/ DHQP
 Ms. Amanda Overholt, CDC/ DHQP
 Ms. Danielle Palms, CDC/ DHQP
 Ms. Kaeanne Parris, CDC/ DHQP
 Dr. Priti Patel, CDC/ DHQP
 Dr. Kiran Perkins, CDC/ DHQP
 Dr. Joe Perz, CDC/ DHQP
 Ms. Ruby Phelps, CDC/ DHQP
 Dr. Daniel Pollock, CDC/ DHQP
 Ms. Jan Ratterree, CDC/ DHQP
 Ms. Meredith Reagan, CDC/ DHQP
 Ms. Cathy Rebmann, CDC/ DHQP
 Dr. Sujan Reddy, CDC/ DHQP
 Ms. Kristin Roberts, CDC/ DHQP
 Ms. Georgeanne Ryan, CDC/ DHQP
 Dr. Melissa Schaefer, CDC/ DHQP
 Dr. Issac See, CDC/ DHQP
 Dr. Lynne Sehulster, CDC/ DHQP
 Ms. Kathy Sieber, CDC/ DHQP
 Dr. Arjun Srinivasan, CDC/ DHQP
 Ms. Erin Stone, CDC/ DHQP
 Dr. Nicola Thompson, CDC/ DHQP
 Ms. Abbigail Tumpey, CDC/ DHQP
 Dr. Snigdha Vallabhaneni, CDC/ NCEZID/
 DFWED/ MDB
 Ms. Wendy Vance, CDC/ DHQP
 Ms. Ellen Wan, CDC/ DHQP
 Dr. J. Todd Weber, CDC/ DHQP
 Dr. Carrie Whitworth, CDC/ DHQP
 Ms. Sarah Wiley, CDC/ OID
 Ms. Sarah Yi, CDC/ DHQP

Members of the Public

Dr. Jim Arbogast, Gojo
 Ms. Kay Argroves, American Association of
 Nurse Anesthetists
 Mr. Nick Austerman, Bard Medical
 Mr. Steve Brash, HCA Hospitals, Richmond.
 Ms. Nicole Bryan, CSTE
 Dr. Russ Castioni, 3M
 Ms. Kendra Cox, Cambridge Communications,
 Training, & Assessments
 Ms. Pamela Falk, Northside Hospital
 Mr. Hudson Garrett, PDI
 Ms. Maryellen Guinan, America's Essential
 Hospitals
 Ms. Amna Handley, GA Pacific
 Ms. Lori Harmon, Society of Critical Care
 Medicine
 Ms. Linda Homan, Ecolab
 Ms. Eve Humphries, Society of Healthcare
 Epidemiologists of America
 Dr. Jesse Jacob, Emory University
 Mr. Robert Jones, Goldshield/ Energy and
 Environmental
 Dr. Jason Kane, Society of Critical Care
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 MS. Rachel Long, BD
 Dr. Peter Nichol, Medline Industries, Inc.
 Ms. Renee Odehnal, Ethicon
 Mr. Pat Parks, 3M
 Ms. Silvia Quevedo, Association of
 Professionals in Infection Control
 Ms. Maria Rodriguez, Xenex
 Dr. Michelle Stevens, 3M
 Ms. Rachel Stricof, Council of State and
 Territorial Epidemiologists
 Ms. Lisa Tomlinson, APIC
 Ms. Kathy Warye, Infection Prevention Partners

Executive Summary

The Division of Healthcare Quality Promotion (DHQP), National Center for Emerging and Zoonotic Infectious Diseases (NCEZID), Centers for Disease Control and Prevention (CDC), US Department of Health and Human Services (HHS) convened a meeting of the Healthcare Infection Control Practices Advisory Committee (HICPAC) on March 31, 2016 in Atlanta, Georgia. The Designated Federal Official (DFO) and Chair confirmed the presence of a quorum of HICPAC voting members and *ex officio* members.

The meeting was called to order at 9:07 a.m. on March 31, 2016. Dr. Denise Cardo provided updates from DHQP, particularly focusing on antimicrobial resistance (AMR). Dr. Suzanne Schwartz and Ms. Catherine Wentz, US Food and Drug Administration (FDA), shared updates on FDA's ongoing efforts regarding the public health concern of Nontuberculous *Mycobacterium* (NTM) infections associated with heater-cooler devices and efforts pertaining to duodenoscope reprocessing and instructions. HICPAC member Dr. Lisa Maragakis led a discussion on the progress of the HICPAC workgroup on Endoscope Reprocessing, which is drafting and revising an Essential Elements document to provide assistance to institutions that have endoscope reprocessing programs. Drs. Michael Bell and M. Shannon Keckler presented outlines for documents to describe device considerations for healthcare facility purchasing departments. Mr. Terrell Cunningham, FDA, briefed HICPAC on the current status of FDA's review and regulation of surgical/isolation gowns. HICPAC member Dr. Jan Patterson presented the progress of the HICPAC Antibiotic Stewardship Workgroup on antibiotic guidelines. Ms. Erin Stone and Dr. Tom Talbot, HICPAC member, presented updated data and an updated draft recommendation regarding Chlorhexidine Gluconate-Impregnated (CGI) Dressings for Intravascular Catheter Exit Sites. Drs. David Kuhar and Kathleen Irwin described progress on an update to the 1998 *Guideline for Infection Control in Healthcare Personnel*. There was a public comment period. HICPAC *ex officio* members and liaison representatives provided written and verbal updates.

HICPAC stood in recess at 5:23 p.m. on March 31, 2016. The next HICPAC meeting will be held on July 14-15, 2016, in Atlanta, Georgia.

DEPARTMENT OF HEALTH AND HUMAN SERVICES
CENTERS FOR DISEASE CONTROL AND PREVENTION
National Center for Emerging and Zoonotic Diseases
Division of Healthcare Quality Promotion

Healthcare Infection Control Practices Advisory Committee (HICPAC)

March 31, 2016
Atlanta, Georgia

DRAFT Minutes of the Meeting

The Division of Healthcare Quality Promotion (DHQP), National Center for Emerging and Zoonotic Infectious Diseases (NCEZID), Centers for Disease Control and Prevention (CDC), US Department of Health and Human Services (HHS) convened a meeting of the Healthcare Infection Control Practices Advisory Committee (HICPAC) on March 31, 2016, at the Tom Harkin Global Communications Center at the Centers for Disease Control and Prevention, 1600 Clifton Road NE, Atlanta, Georgia.

Thursday, March 31, 2016

Welcome and Introductions

Jeff Hageman
Division of Healthcare Quality and Promotion
National Center for Emerging and Zoonotic Infectious Diseases
Centers for Disease Control and Prevention
Designated Federal Official, Healthcare Infection Control Practices Advisory Committee

Mr. Jeff Hageman called the meeting to order at 9:07 a.m. He welcomed HICPAC members, *ex officio* members, and liaison representatives. He noted the following changes to HICPAC membership:

- Dr. Michael Howell, the former HICPAC liaison representative from the Society of Critical Care Medicine (SCCM), has rotated onto HICPAC as a member.
- Ms. Loretta Fauerbach is a new HICPAC member.
- Dr. Deborah Yokoe is serving as co-chair of HICPAC with Dr. Daniel Diekema.
- Mr. Hageman conducted a roll call. A quorum was present. HICPAC members disclosed the following conflicts of interest:
 - Dr. Diekema has received research funding from bioMérieux.
 - Dr. Jan Patterson's spouse conducted research in fungal disease and has served as a consultant to, or conducted research with, Merck, Astellas Pharma, and Toyama Chemical Company.
 - Dr. W. Charles Huskins has received research support from GOJO Industries and has served as an advisory board member for Genentech.
 - Dr. Thomas Talbot's spouse is a vaccine researcher who has received funding from Sanofi Pasteur, MedImmune, Gilead Sciences, and Novartis.
 - Dr. Lisa Maragakis receives research funding from Clorox/UltraViolet Devices, Inc. (UVDI) for studies of ultraviolet (UV) light.

- Ms. Lynn Janssen's spouse works for a biotech company developing vaccines and immunologics.

CDC Updates: Division of Healthcare Quality Promotion (DHQP)

Denise Cardo, MD

Director, Division of Healthcare Quality Promotion

National Center for Emerging and Zoonotic Infectious Diseases

Centers for Disease Control and Prevention

Dr. Denise Cardo welcomed HICPAC and provided updates on CDC's plans regarding antimicrobial resistance (AMR) and the funds allocated for CDC in the fiscal year (FY) 2016 budget related to antibiotic resistance (AR). The budget initiative is an example of how evidence can lead to policy, and then to a budget initiative with opportunities to expand programs that are already being implemented.

Vital Signs is a monthly publication with CDC's *Morbidity and Mortality Weekly Report (MMWR)*. Each of CDC's "Winnable Battles" is featured in an issue of *Vital Signs* in a specific month. Healthcare-associated infections (HAIs), which include AMR, were featured in March. DHQP uses the *Vital Signs* mechanism to make a case for infection prevention and for the importance of engaging a range of different groups in making a difference in the problem of HAIs.

- The first *Vital Signs* on HAIs focused on successes in preventing central line-associated bloodstream infection (CLABSI) and on the lives that were saved. The issue also called for more action to continue to work on prevention.
- The next issue highlighted *Clostridium difficile* (*C. diff*) infections and their relation not only to infection control but also to antibiotic use.
- The topic of the third *Vital Signs* was emergence of carbapenem-resistant *Enterobacteriaceae* (CRE), an issue that was well-known to experts but may not have been perceived by the broader healthcare community or public as an emerging threat.
- After presenting a series of HAI-related problems, the next *Vital Signs* presented a solution: promoting stewardship programs. This publication represented the first time that CDC clearly recommended antibiotic stewardship programs for all hospitals. DHQP worked closely with the American Hospital Association (AHA) and other partners to ensure that the publication was not isolated, but served to add CDC's voice to other partners' voices to facilitate implementation of stewardship programs.
- The next *Vital Signs* related to a coordinated approach to prevention, particularly the importance of working not only within but also across healthcare facilities to prevent the transmission of multidrug-resistant organisms (MDROs) and *C. diff*.

The most recent *Vital Signs* focused on integrating information from previous *Vital Signs* issues. The solutions proposed in the prior issues focused on programs and administrative strategies. This issue focused on resistant bacteria as a cause of HAIs. The publication described progress related to HAIs, but also noted that a large percentage of infections in healthcare are caused by resistant pathogens. The solutions require improvements in both horizontal strategies that are important for preventing a range of HAIs as well as vertical strategies aimed at preventing transmission of specific AR pathogens. This *Vital Signs* was aimed at informing the broad healthcare community beyond just infection control experts, , the general public, and policymakers.

Because the overall burden of AR needed to be defined, DHQP used available data to create the [“AR Threat Report.”](#) The report clarifies that the numbers are not precise and are a low estimate of the number of infections. The report was critical to highlight the magnitude of the AR problem for different groups, such as policymakers, and to engage them to be part of the solution. The solution involves not only the creation of new antibiotics. In addition, the report presented a framework for preventing infections, preventing the spread of infections, tracking infections, improving antibiotic use, and developing new drugs and new diagnostics.

DHQP works closely with federal partners and partner professional groups. The President’s Advisory Committee on Antimicrobial Resistance, which included public health and healthcare experts as well as other participants, created the [National Action Plan for Combating Antibiotic Resistant Bacteria \(CARB\)](#). The plan has five specific goals:

- Slow the emergence of resistant bacteria and prevent the spread of resistant infections
- Strengthen national one-health surveillance efforts to combat resistance
- Advance development and use of rapid and innovative diagnostic tests for identification and characterization of resistant bacteria
- Accelerate research to develop new antibiotics and alternative therapeutics and vaccines
- Improve international collaboration and capacities for disease prevention and surveillance and antibiotic research and development

CARB also has specific goals for reducing and preventing infections in the next five years. Monitoring progress toward these goals is important and helps to provide insight if certain goals are not being met. CDC’s role in CARB is to:

- Detect and respond to resistant pathogens
- Prevent the spread of resistant infections
- Encourage innovation for new strategies

CDC developed the [AR Solutions Initiative](#) and requested \$264 million to address the agency’s goals related to AR. CDC’s appropriation in FY ’16 was \$160 million which represents a significant increase over previous years. The FY ’17 budget includes an additional \$40 million for CDC to expand its programs further. It is important to note that the funding is not for new programs but instead will be used to expand existing programs that are making a difference. CDC’s overall approach incorporates urgent threats such as CRE, *C. diff*, and *Neisseria gonorrhoeae*, as well as strategies for serious infections such as Methicillin-resistant *Staphylococcus aureus* (MRSA) and other MDROs.

Regarding “detect and respond,” CDC’s approach includes laboratory as well as public health activities, and the response includes identification as well as containment of infections. “Prevent” focuses on a coordinated approach, and “innovate” includes new diagnostics and new ways to prevent HAIs.

The budget will support expansion of funding to state and local health departments. The Recovery Act allowed for the creation of HAI programs in state Health Departments, and they will continue to be funded through the Prevention Fund of the Patient Protection and Affordable Care Act (ACA). The support can be expanded to address AR. States will be eligible to receive

funding for more expertise in analyzing data and in responding to resistance issues at the state and local levels. State laboratories in all 50 states will be eligible to receive funding to improve capacity to detect CRE. Further, up to 25 states will receive additional funds to focus on prevention strategies with a coordinated approach. Data from the Prevention Epicenters show that if healthcare systems and facilities do not work together, then it is difficult to prevent HAIs. This work will take place with a network of facilities and expert groups and will be evaluated for its impact.

The laboratory network will also be expanded. Up to seven regional laboratories in the PulseNet regions will be funded to build capacity to address resistant pathogens. The work varies by pathogen and includes identifying mechanisms of resistance, as well as responding to outbreak events, implementing containment strategies, and screening patients. This support cannot be provided by hospitals or health departments; therefore, the regional laboratories will be funded to provide those services. The laboratories will work closely with academic centers and clinical laboratories on specific projects that respond to trends and problems.

The HAI Emerging Infections Program (EIP) also will expand to include more pathogens, including more multidrug resistant (MDR) gram-negatives. Additional settings will be included. For instance, work on MRSA work will expand to include community as well as healthcare settings. Plans for the future will incorporate assessments of extended spectrum beta-lactamases (ESBLs) and urinary tract infections (UTIs) in the community and their potential impact on healthcare. Pilots will be conducted in these areas before adding the work to the entire EIP. Annual prevalence surveys will continue not only in acute care, but also in long-term care. The HAI EIP will also work on sepsis. The EIP can add to understanding of risk factors and prevention strategies.

Innovation is critical for HAI prevention. Academic partners are vital to innovation. The Prevention Epicenters and other mechanisms provide opportunities to fund academic groups and healthcare systems to improve antibiotic use. Social networking tools will help implement coordinated approaches to stop the spread of AR. Other initiatives include improving sepsis recognition and early detection, particularly in partnership with SCCM and other partners. Electronic health records (EHRs) are potentially important tools to define appropriate use, and the healthcare environment can also play a critical role in the transmission and prevention of infections. The human microbiome is another innovative area for exploration.

The isolates housed at CDC can help industry and academic partners to develop new diagnostic tools, treatment tools, and vaccines. With the US Food and Drug Administration (FDA), the [AR Isolate Bank](#) has been developed. The US Department of Defense (DoD) also has a large collection of isolates, but the FDA-CDC bank is targeted for unique resistance that industry and academic partners can use. The bank has approximately 260 isolates.

Regarding implementing antibiotic stewardship programs and practices, new diagnostic tools are an important means for better detection of infections, improving use of antibiotics, and adding to knowledge regarding sepsis. CDC considers the entire spectrum of care to protect patients from infections, including HAIs, sepsis, and viral infections. Several healthcare systems receive CDC funding to implement strategies to improve use and improve outcomes. The systems are encouraged to use the antibiotic use [\(AU\) module](#) of the National Healthcare Safety Network (NHSN). In outpatient settings, stewardship work incorporates using the data and working with partners to implement concrete interventions. Stewardship efforts are just beginning in long-term care, but CDC is already working with partners to determine how best to

move forward with programs as well as concrete strategies to improve antibiotic use in those settings. CDC is funding healthcare systems, health departments, academic groups, and professional and public health organizations in these areas.

The concept of antibiotic stewardship also incorporates sepsis. The two issues have been perceived as contrary, but they should be messaged together. CDC is considering not only how to improve antibiotic use but also how to better detect infections and create strategies for reassessing antibiotic use. Education is important for patients, especially in the outpatient settings. It is also important for clinicians and a range of different groups to improve use.

CDC is building upon opportunities to work with different groups on the early detection and management of sepsis. Some professional organizations and groups have been working to improve antibiotic use and others have been working on early detection of sepsis. The work of these two groups may not have been optimally integrated in the past. There are opportunities to work on these issues holistically and to help patients. CDC is launching an educational campaign that unifies the messages of sepsis and appropriate antibiotic use:

- “Think sepsis”
- Collect laboratory cultures
- Encourage clinicians to “act fast”
- Encourage clinicians to reassess the need for a specific antibiotic, or for any antibiotic, 48-72 hours later
- Prevent future infections: if infections are prevented, there will be no sepsis

Based on the gaps identified by partners, the campaign considers the entire cycle. CDC and DHQP are conducting more activities related to sepsis, including the following:

- Better understand the epidemiology of the patient and the risk factors that can lead to better prevention, sometimes primary prevention
- Track sepsis infections for prevention activities to determine the impact of successful interventions
- Promote prevention, early recognition, and use of effective and appropriate antibiotics
- Work with various groups to conduct and refine campaigns, building on opportunities to help partners work together with facilities to implement infection prevention and stewardship activities

Discussion Points

There may be state-to-state and region-to-region variation in existing capacity. As CDC moves resources out, individual states’ ability to utilize the funding most effectively or to increase capacity may need to be assessed. For instance, the Targeted Assessment for Prevention (TAP) reports from NHSN focus on the most quickly and easily achievable goals that require limited effort and resources for preventing infections in hospitals. Nationally, it may be important to focus on geographic areas that are in most need of additional resources.

Dr. Cardo agreed that capacity varies by state. A group in DHQP is assessing state programs not only in terms of whether they prevent infections but also regarding the infrastructure that is needed to do the work. The health departments should work with academic centers in order not

to duplicate efforts and to leverage synergies. States can apply for direct assistance in making these connections and building capacity in prevention, detection, and response.

The overall program has aggressive targets. HICPAC asked about metrics. Some MDROs in institutions are real infections, while some results are related to testing behaviors and the type and sensitivity of diagnostics that laboratories use. The problem can be addressed with prevention and education of clinicians regarding appropriate testing.

Dr. Cardo said that the metrics for the budget initiative should be aggressive. Payment metrics are different. DHQP is setting goals for the national initiative to help assess where progress is being made and why targets are not being met. The evaluation will help to assess whether absence of progress around *C. diff.*, for example, reflects deficiencies around antimicrobial stewardship or increasing community transmission. Specific metrics for states may be developed at a later time.

FDA Device Updates: Flexible Endoscopes and Heater Coolers

Suzanne Schwartz, MD, MBA

Catherine Wentz, MS

Center for Devices and Radiological Health

US Food and Drug Administration

Dr. Suzanne Schwartz and Ms. Catherine Wentz updated HICPAC on FDA's ongoing efforts regarding the public health concern of Nontuberculous *Mycobacterium* (NTM) infections associated with heater-cooler devices. An FDA advisory committee meeting on this topic will be convened on June 2-3, 2016. They also updated HICPAC on FDA's work regarding flexible endoscopes. FDA welcomes HICPAC's input and advice regarding its multi-pronged approaches to these problems.

Dr. Schwartz explained that in May and June of 2015, based on early signals observed in Europe, CDC and its European counterpart reached out to FDA regarding a potential association between heater-cooler devices and NTM infections in patients who had undergone cardiac surgery. Reports to FDA regarding heater-cooler devices are classified into two areas: 1) patient infections, and 2) device contamination.

FDA receives user facility reports, voluntary reports, and manufacturer-submitted reports. When a safety notice is issued by FDA or its regulatory partners outside of the US, it is typical for reporting to increase due to increased awareness. Without this awareness in the healthcare provider community, FDA is handicapped by limited information, which in turn inhibits the agency's ability to ascertain the breadth and scope of the concern and to enact a timely investigation and response. FDA relies on the help of HICPAC and its partners, including professional societies based in hospitals, to raise the level of awareness to yield a fuller picture of a concern. FDA's approach to this investigation is broad. The investigation includes all heater-cooler devices that are regulated for use in cardiac surgery and is not focused solely on a single manufacturer's product.

Ms. Catherine Wentz is an engineer in FDA's Division of Cardiovascular Devices, which reviews heater-cooler devices and clears them for market. She described heater-cooler devices, which provide heated and/or cooled water to heat exchange devices for oxygenators and for cardioplegia heat exchanges. These devices can also provide temperature-controlled water to

heating and cooling blankets. The devices are FDA Class II and are cleared under two regulations:

- Thermoregulating devices, which include blankets
- Cardiopulmonary bypass temperature control devices, which feed temperature-controlled water to the heat exchangers in the bypass circuit

The heater-cooler devices are in the extracorporeal circuit and feed the two heat exchangers. The heater-cooler device is usually located close to the perfusion circuit, or heart-lung machine, which is within the operating room (OR), but outside the sterile field.

Heater-cooler devices have been on the market since the 1960s. For Class II devices, the sponsor must submit information to the FDA to demonstrate that the device can be compared to another device that is currently on the market, or the “predicate device.” The sponsor also must demonstrate that the device meets certain performance criteria called “special controls.” The FDA regulatory review for these devices generally includes:

- Review of device technology
- Performance and labeling as compared to the predicate device
- A determination of whether any differences between the devices can affect safety or effectiveness

The labeling review includes a review of the cleaning and disinfection procedure for the unit. Since the temperature-controlled water circuit of a heater-cooler device is a closed circuit with no intended patient contact and the device is not in the sterile field, the health risk associated with these devices for patients was considered to be low. As such, in the past, the disinfection procedures were not reviewed in detail; rather, the FDA relied on the Quality Systems Regulations in its Office of Compliance regarding validation of the procedures. The sponsor must have validated data in its files for these procedures. The possibility of aerosolization with heater-cooler devices was not a consideration until recently.

Since device contamination appears to be a recurring issue, FDA is actively working with manufacturers to appropriately validate their cleaning and disinfection procedures, taking into consideration issues relating to human factors, to demonstrate that the labeled procedures minimize contamination and that the procedures can be feasibly, consistently and effectively followed by the anticipated end user. It is important to note that the cleaning and disinfection of heater-cooler devices outside the manufacturer’s labeled procedures may result in a damaged device and is not recommended.

Mycobacterium chimaera is a relatively new species within the non-tuberculous Mycobacteria (NTM) grouping which consists of 150+ species. *Mycobacteria* can be divided into two groups: NTM and *Mycobacterium tuberculosis*. This investigation focuses specifically on *Mycobacterium chimaera* (*M. chimaera*) which is an NTM. While *M. chimaera* has been identified in many of the cardiac surgical patient infections to date, there also have been clusters of infections due to other NTM species such as *Mycobacterium abscessus* (*M. abscessus*).

NTM can be further categorized into rapid growers, which grow on solid media in 5 to 10 days, such as *M. abscessus*; and slow growers, which may grow on solid media in 6 to 8 weeks, such as *M. chimaera*. All of these waterborne bacteria have the ability to form biofilms. This point is

important to contamination, as once biofilm has formed inside the tank or the circuit, cleaning and disinfection of the device becomes difficult, if not impossible.

NTM is widespread in nature. It is found in natural and tap water, in soil, and even in some surgical solutions. Based on the infections being reported, NTM are likely being spread through aerosolization. Some predisposing patient factors that may contribute to the likelihood of infection include:

- Altered local or systemic immunity
- Structural factors, such as chronic obstructive pulmonary disease (COPD) or cystic fibrosis (CF)
- Surgical procedures with an open cavity, such as cardiopulmonary bypass or valve replacement

FDA's response has been multi-pronged over the past 10 months, given that an increasing number of NTM infections have been identified and reported by healthcare facilities through retrospective review of their patients who were exposed to contaminated heater-cooler devices during cardiac surgery. The reviews, in some cases, go back as many as four years and this extended scope in case finding is necessary because NTM infections can take years to develop into a symptomatic infection. FDA continues to receive reports of device contamination in spite of adherence to manufacturers' instructions for the cleaning and disinfection of these devices. The FDA response has incorporated research regarding:

- Design of the device
- Environment in which the device resides
- "Human factors" or usability aspects associated with cleaning and disinfecting

FDA has also conducted outreach to various organizations, agencies, and experts.

FDA has studied many facets of the surgical procedure, including:

- Water contamination
- Transmission of NTM into the OR
- Device design considerations
- OR design considerations
- Patient considerations

The investigations into water contamination focus on possible mechanisms that could enable NTM to reach the water tanks and contaminates the heater-cooler units.

- Tap water contains NTM naturally. These devices need to be filled, re-filled, rinsed, cleaned, and "topped off." If any of these steps utilize tap water rather than sterile water, NTM can be introduced into the device.
- The manufacturing line should be considered, as NTM could be in the water used to clean or rinse the devices as part of the manufacturing process.
- The devices are connected to external components, such as tubing and blankets, which may be reusable. Even if the heater-cooler device is disinfected, re-contamination will occur when it is reconnected to these reusable components if the circuit is contaminated.

- Access to the water tank and circuit may be limited. If full access is not possible, the tank may not be able to be physically scrubbed. If there is biofilm in the tank, mechanical scrubbing will most likely be necessary to eliminate the biofilm.
- FDA is addressing the cleaning and disinfection procedures proposed by the manufacturers to ensure that the procedures are adequate and validated to reduce contamination of the heater-cooler devices and aerosolization of organisms that can lead to patient infections.

One of the original papers suggesting aerosolization of NTM from heater-cooler devices was published by Dr. Hugo Sax in March 2015. Following that publication, a paper was published by Dr. J.O. Falkinham describing the hydrophobicity of NTM and its behavior in the context of heater-cooler devices. Dr. Falkinham cites a 1983 paper, which states that “hydrophobic mycobacterial cells are concentrated on the surface of air bubbles rising in water columns. When the air bubbles reach the surface, they burst, and water droplets are ejected into the air. Relative to the concentration of mycobacteria in the water, the concentration in the ejected droplets are 1,000 to 10,000-fold higher.” If there is aerosolization inside the water tanks and some communication between the tank and the OR, there is the potential for NTM to reach the OR environment.

FDA is pursuing a number of device design considerations that may contribute to tank contamination and/or aerosolization, including:

- Devices that use ice: is sterile water or tap water used to make the ice?
- Level of agitation inside the water tank creating air bubbles, including mixing components, pumps, and the return water circuit inlet back into the tank. The air bubbles collect hydrophobic NTMs, which burst upon reaching the surface of the water in the tank and create aerosolized NTMs within the tank.
- Water tanks are not usually sealed or airtight: depending upon the design of the unit, the aerosols in the water tank can find their way into the casing of the heater-cooler unit, where cooling fans located within the unit can facilitate their transmission of these aerosols into the OR
- The orientation of the vent(s) on the devices may or may not direct the fan exhaust toward the patient or the sterile field. The exhaust from cooling fans also may play a role in the airflow within the OR, possibly facilitating movement of the aerosolized NTM into the sterile field
- Access to the water tank and physical cleaning of the tanks prior to disinfection procedures that alone cannot remove biofilm may be necessary to assure proper disinfection of the tanks and internal water circuits.

In order to address these questions, FDA has sent information request letters to all manufacturers of these devices and is reviewing the information that has been returned. Regarding OR environment considerations, one limited study was conducted on one heater-cooler unit. It raised questions regarding the potential for the exhaust airflow from the heater-cooler unit to disrupt the protective laminar air flow above the patient in the OR. The study suggests that disruption of the protective laminar airflow may create a pathway for aerosolized NTM to find its way into the sterile field, and ultimately into the patient’s open chest cavity. While this study was limited, it does raise questions about other OR environmental factors, such as airflow, that may play a role in mitigating patient infections.

FDA is also consulting with epidemiologists who have studied the general effectiveness of infection control measures implemented in the OR during a surgical procedure, including:

- Laminar flow rate
- Positive pressure maintained during a procedure
- Cleaning of the OR between cases
- Infection control measures taken by the surgical team during the procedure

These areas could be reviewed and potentially improved. Patient considerations are also important. To date, most of the reported infections are in cardiothoracic or cardiovascular patients undergoing an open chest procedure requiring the use of an extracorporeal circuit. Many of these patients received a sterile implant, such as heart valve. The patients' general health may also contribute to infection susceptibility.

Many challenges are associated with this multi-factorial problem.

- It is not feasible for these devices to be sterile.
- There are many OR environment considerations as well as hospital infection control procedure and patient considerations.
- NTM is fairly ubiquitous and, locating the source of NTM leading to infection is challenging.
- It is not clear whether there is an acceptable level of contamination at which a device can still be used safely. For instance, if aerosols can be reduced or eliminated from the unit, can the circuit water safely maintain some level of contamination?
- There are challenges associated with validating the cleaning and disinfection procedures and what might represent "worst-case" testing. It is not clear how real-world use can be mimicked in laboratories for testing. Which microbe or microbes should be monitored and what is an acceptable output or contamination level?
- Heater-cooler units are a capital expense, currently with a service life of approximately 10 years. If they become contaminated beyond an acceptable level, alternatives are needed for these lifesaving devices. Unless contaminated units can be reliably disinfected, purchase of new units may be necessary.
- Patient notification is a challenge, including what patients should be told regarding the risks prior to a procedure and whether patients who have already undergone a cardiac surgery should be stratified and notified based on a reliable risk scale.

The FDA's ultimate objective is to protect patients from infection. Based on the investigations, theories, limited data, suppositions, and common sense, the agency has identified some short-, mid-, and long-term goals which are being pursued in parallel to reach the ultimate objective.

Short-Term Goals: Can be enacted immediately and reduce the possibility of infection without compromising device performance, device structural integrity, or patient safety:

- Location of heater-cooler devices in relation to the patient and sterile field
- Orientation of heater-cooler vents in relation to the patient and sterile field
- Directing or channeling the exhaust from heater-cooler device away from the patient and sterile field
- Performing an evaluation of the OR environment with respect to aerosol dispersion into the surgical field
- Review hospital infection control procedures for any improvements that can be made

Mid-Term Goals:

- Mitigation of aerosols from the heater-cooler devices into the OR. FDA is working with manufacturers on design aspects of their devices to prevent aerosolization of NTM into the OR.
- Studies to determine whether airflow in the OR can be manipulated to reduce the possibility of aerosols reaching the sterile field

Longer-Term Goals:

- Identifying cleaning and disinfection methods that will prevent biofilm formation and maintain contamination levels in the tank and water circuit at acceptable levels.

Dr. Schwartz commented on Dr. Cardo's emphasis on building coalitions and bridges and working collaboratively. Solving the problems associated with heater-cooler devices and NTM will require awareness and partnering across federal agencies as well as state, local, private sector, academic, and clinical partners. FDA has proactively engaged with different entities and organizations.

The Medical Product Safety Network (MedSun) through FDA's Center for Devices and Radiological Health (CDRH) brings opportunities for direct work and "deep dive" discussions with individual healthcare facilities that have been impacted by, or are concerned about possible impacts of, these issues. FDA also works with perfusionist societies, the Society for Healthcare Epidemiology of America (SHEA), the Infectious Diseases Society of America (IDSA), and other organizations. Other important partners include CDC, state departments of health, and regulatory agencies outside the US, particularly because of the lessons learned from signals observed overseas. The open exchange of information is critical to a multifaceted approach to the challenge.

In October 2015, FDA issued a safety communication that provided FDA's current understanding of the matter as well as short-term recommendations to provide immediate mitigation to reduce patient risk. FDA stands by the recommendations in that communication and is committed to revising and updating the recommendations as more information is gathered.

FDA has enforcement and compliance authority. As issues are identified related to lack of adherence to regulations and other problems, enforcement can occur. A warning letter was sent to one of the heater-cooler device manufacturers in December 2015. The warning letter, which is publicly available in redacted form on FDA's website, includes an import alert for that product, with an exemption for medical necessity. The problems with heater-cooler devices are potentially systemic; that is, the same concerns might involve the devices of other manufacturers.

A webpage on heater-cooler devices was released in March 2016. This approach allows FDA to provide updates in a timely manner and share them quickly with the public and healthcare provider communities. The agency is committed to maintaining those updates as more information is available. The page includes an information section for patients to help them make informed decisions and to provide guidance regarding conversations with their healthcare providers. The webpage is available at:

<http://www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/CardiovascularDevices/Heater-CoolerDevices/default.htm>

The Medical Device Advisory Committee meeting is public and will convene on June 2-3, 2016. The standing Circulatory System Devices Panel which includes clinical experts in cardiovascular disease (e.g., cardiologists, cardiac interventionalists and cardiothoracic surgeons) is being expanded to assure that experts in infectious disease, infection control, and epidemiology, among others will contribute to the discussions, questions, and recommendations.

Some of the FDA recommendations in the Safety Communication and on the webpage include:

- Strictly adhere to the cleaning and disinfection instructions provided in the manufacturer's device labeling. Some facilities go above and beyond thinking that more is better but that approach is not advised, especially when parts of these devices are susceptible to corrosion and other related issues. Manufacturers' instructions and labels change frequently so should be monitored by the facility to ensure that they have the most recent version of the manufacturers' instructions and labeling.
- The heater-cooler device exhaust vent should face away from the surgical field in order to minimize the potential for patient exposure.
- Facilities should establish regular cleaning, disinfection and maintenance schedules for heater-cooler devices according to the manufacturer's instructions.
- Facilities should immediately remove from service any heater-cooler devices that show discoloration or cloudiness in the fluid lines/circuits, as it may be indicative of bacterial growth.
- Consider performing environmental, air, and water sampling and monitoring if heater-cooler contamination is suspected. There is variability across the country, however, regarding the feasibility and practicality of being able to carry out the sampling. The information that can be yielded from the tests is very helpful to FDA.
- If bacterial contamination of a heater-cooler device is suspected, or if there have been patient infections, facilities should not only notify the manufacturer, but also FDA through the MedWatch reporting system or other means. FDA seeks as much as information as possible, from across the country and from facilities that use different types of devices.

The main topic areas to be discussed at the upcoming advisory committee meeting include:

- Effectiveness of cleaning and disinfection methods for heater-cooler devices
- Premarket data and information needed in order to demonstrate validation of cleaning and disinfection of heater-cooler devices to support labeling and technical instructions
- Protective measures and risk mitigations that can improve upon and enhance patient safety during procedures where these devices are used, knowing that the devices are used in critical, often life-saving, procedures
- Identifying risk stratification schema that will help inform guidelines for notifying patients who may have already been exposed to NTM during prior cardiac surgeries

Flexible Endoscope Update

Dr. Schwartz reminded HICPAC that at the July 2015 meeting, she presented recommendations from FDA's May 2015 Advisory Committee meeting on concerns related to duodenoscopes. Since then, there has been a great deal of activity and action pertaining to duodenoscope reprocessing and instructions.

In August 2015, FDA issued a “supplemental measures” safety communication while the agency continued to work on the problem. This communication provided healthcare facilities with options to consider for enhancing and improving the safety margin for use of duodenoscopes for important endoscopic retrograde cholangiopancreatography (ERCP) procedures. FDA issued warning letters to all three duodenoscope manufacturers in the summer of 2015 and ordered all of the manufacturers to perform post-market surveillance studies. FDA continues to work with each of the duodenoscope manufacturers to ensure validation of their cleaning and high-level disinfection protocols for manual reprocessing. At this point, all three manufacturers have fully validated their reprocessing instructions and have issued safety communications with the new, revised instructions for use.

FDA has taken a parallel path to address the automated endoscope reprocessors (AERs) to ensure that the validation for use of those devices with duodenoscopes is equally as robust. FDA posted an AER webpage in February 2016 as work continues with each of the AER manufacturers. The webpage will continue to provide updates on which devices have completed testing, FDA review, and and noted to be adequate in passing acceptance criteria.

Recently, the 510(k) premarket notification for the Olympus TJF-Q180V closed elevator channel duodenoscope was cleared for marketing, along with a recall of the current Olympus TJF-Q180V duodenoscopes. Through this field safety correction, Olympus has committed to a phased approach to the recall over six months so that it will be completed by August 2016. The scopes that are in the market will be recalled so that the entire elevator mechanism can be replaced with the newly-designed mechanism that has been reviewed and approved by FDA. The devices will be redistributed. Olympus has also committed to annual servicing and testing of the devices.

Discussion Points

Regarding heater-cooler devices, HICPAC commented on anxiety regarding whether the short-term interventions will be adequate to prevent patients from ongoing exposure. Some of this anxiety is linked to a lack of understanding regarding the epidemiology. HICPAC asked whether specific information is available from FDA’s studies to date regarding why *M. chimaera* is a particular problem, whether the isolates are clonal, and evidence for contamination at the manufacturer level versus the point-of-care usage sites.

Dr. Schwartz answered that the epidemiology is the key question. FDA does not have a full picture to address the epidemiology and has embarked on the campaign to learn about what is happening within various clinical facilities inside and outside the US. More information will be publicly available by June 2016. The information that FDA has is driving the short-term mitigations, which the agency believes to be appropriate in recognition of anxiety about the devices. Patients should not be put at risk. There is a need to update and revise recommendations rapidly as more information comes to light. The device that has received the most attention has 80% to 90% of the global market share of these devices. Therefore, the detection associated with that device will automatically be higher. FDA does not have a sense whether facilities that use other devices are looking retrospectively to learn about contamination or infections associated with NTM in cardiac patients. The picture is not full enough to make epidemiologic associations. Help is needed from professional societies and others to “pull this picture together.”

It has become clear that case-finding, the critical first step in an outbreak investigation, is a major problem. Infectious disease and other clinicians do not routinely order acid-fast bacillus (AFB) cultures in patients based on a prior history of exposure to cardiac bypass. There is an “information vacuum” in terms not only of how extensive the problem is, but also for guidance on moving forward. HICPAC suggested that interim, tiered guidance is needed for institutions based upon whether they are conducting surveillance on their own heater-cooler units, whether they have detected contamination, whether the cultures have an acceptable negative predictive value, and suggesting next steps for patient notification. A uniform strategy for the country may be needed for case finding and patient notification. The “iceberg below the surface” of this problem is large and concerning.

In response to a question from HICPAC about the frequency and rate of infections, Dr. Schwartz answered that FDA does not have a sense of the frequency or rate of infections. Detection depends on facilities and organizations conducting and providing reports on retrospective evaluations that find links or associations. The reports often do not provide enough substantive information to understand the adverse event or injury. FDA is requesting to speak with the institutions that have voluntarily reported to fill the information gaps to patients’ backgrounds and medical histories and to understand whether the infections are related to infected valves, bypass procedures, or other events.

As one manufacturer represents the majority of the global market of heater-cooler devices, HICPAC asked whether the institutions where these infections have occurred have unique attributes, such as their water supplies and cleaning practices, that could shed light on the problem.

Dr. Schwartz answered that insufficient information is available to find a common thread among the institutions. Many facilities have reported because they have a heightened level of awareness and have chosen to conduct the retrospective evaluations. The European regulatory agencies have noted that the level of visibility of this issue is more heightened in certain countries. Most of the reporting has occurred in Europe, where coalitions of different organizations and entities have grown to ensure that the information is distributed and that facilities are doing their retrospective work.

Dr. Bell commented on the idea of observing cloudiness or discoloration in fluid in the system. The system is open and the reservoir is “topped off;” even if sterile water is used, there will be cloudy material in the device. He asked about the appropriate follow-up measures that the FDA guidance recommends after consulting with a hospital’s infection control officials.

HICPAC said that given what is known about these devices currently, the only way to keep patients completely safe is to remove the device from the OR in order to physically separate the air emitting from the device from the air that surrounds the patient. That separation presents a significant challenge, but the devices are lifesaving and required for the performance of cardiac surgery. There does not appear to be a good near-term solution to the problem. Variability around access to laboratories that can reliably identify *Mycobacterium* in hospitals’ water samples is a major limitation.

The US Department of Veterans Affairs (VA) commented on potential contamination of hospitals’ water systems with NTM. Hospital water safety is a hot topic, even more in Europe than in the US. These organisms are fairly resistant to chlorine. Many hospitals are re-oxidizing their water, so the number of *Mycobacteria* may be rising, putting higher concentrations of NTMs in ORs. Hospitals across the US are instituting NTM clinics in response to perceived

increases in disease incidence. The data are not clear, and it is not known whether the mitigation efforts will succeed.

HICPAC observed that heater-cooler devices have been used for decades. There may not be widespread knowledge about, or searches for, NTMs, but there is increased awareness. HICPAC asked about the rates of mortality and morbidity among patients whose cases have been detected. These rates may motivate hospitals to perform more active case finding.

Dr. Schwartz answered that there is not sufficient information to describe incidence. There are more reports of patient deaths outside the US than within the US. Given the denominator of the number of these procedures that are performed, the rate of postoperative NTM infections would be rather small. It is important to weigh the benefits and risks and not to deny patients critical lifesaving procedures. At this stage, there is not enough information to understand what is happening with these patients, some of whom may have undergone surgery years ago. They could have had a fever of unknown origin in the ensuing years and not have received a diagnosis or a workup to elicit the diagnosis of an NTM-related infection or sepsis. FDA looks toward partnering with others in the necessary descriptive epidemiology.

Regarding other types of endoscopes with elevator mechanisms such as endoscopic ultrasound devices, Dr. Schwartz said that FDA has not received reports of adverse events. Features of that device, such as the side-viewing elevator channel, have been a concern. FDA is monitoring other endoscopes carefully as well. In September 2015, FDA issued a safety communication regarding flexible bronchoscopes in response to a signal related to those devices. However, the situation was not entirely analogous to duodenoscopes. Other factors were related to the use of devices with mechanical defects. The design-related challenges of cleaning and reprocessing are not exactly the same for flexible bronchoscopes.

In response to a HICPAC question about the possibility of filtering the exhaust from heater-cooler devices as a short-term measure, Ms. Wentz said that FDA has considered such a strategy. From the FDA perspective, short-term recommendations should avoid device design issues. The agency cannot tell manufacturers how to design their devices and cannot give recommendations to redesign devices. FDA works with manufacturers to identify the design aspects which influence aerosolization. Filtering was discussed with the manufacturers, but it was deemed to be an impractical fix for devices currently in use. The size filter needed at the vent would not permit sufficient airflow to keep the device cool. There may be other alternatives, but adding a filter is not yet a possibility.

HICPAC commented that the field is clamoring for improvements in device design. The recommended short-term measures place the onus on the end user, as infection control departments must create risk mitigation strategies to address patient safety problems associated with an essential, lifesaving medical device that is known to be contaminated and is known to be re-contaminated even after certain mitigation measures. The situation is analogous to the endoscope elevator situation, and probably to other devices. Although the full picture of the epidemiology and of the number of people affected is not yet available, the evidence that is available is compelling. Infections are severe, and patients have died. The work with manufacturers should be accelerated, given that the device design is the root cause of the problem.

Dr. Schwartz said that manufacturers are not only required to address the appropriate validation of the cleaning and disinfection of devices that are in distribution, but also are required to

address device redesign approaches to eliminate or remediate concerns regarding aerosolization. Even if the process is expedited, the fix will not happen quickly. The new design will need to be validated. The different approaches are taking place in parallel. The lessons learned from these experiences will be incorporated into the pre-market evaluation process.

Regarding the idea of using sterile water to make ice, HICPAC noted that even if the ice is sterile, it is still important to follow recommendations to ensure that the ice machine is maintained and cleaned so that it does not become contaminated. That point should be explicit in the guidelines.

HICPAC asked about opportunities to set deadlines for manufacturers to redesign their devices. If there were an alternative, then the problem devices would be eligible for recall, and this would allow FDA to set a timeline to accelerate the redesign process.

Dr. Schwartz agreed, but pointed out that manufacturers need to be able to produce enough devices to satisfy the need. If there is a recall, then manufacturers need to be able to surge production to fill needs during the recall. These supply chain and shortage considerations are important. When FDA decides to remove a device from the market, there are downstream implications for patients. If enough devices are not available to fill the gaps, then short-term measures are needed to ensure that hospital operations can continue without interruption, particularly in case of lifesaving procedures.

The Council of State and Territorial Epidemiologists (CSTE) commented on the public health work of describing the epidemiology of NTMs. There have been dramatic increases of NTMs in recent years, and it is not clear how many of these involve respiratory isolates versus non-respiratory isolates. A pilot study to examine the epidemiology among the respiratory NTMs, working through state public health laboratories or EIP, could look at sterile site specimens with growth of NTM to assess possible etiologies for recent increases, including changes in water supply and the way that water is treated in hospitals.

Update on HICPAC Workgroup and Request for Guidance: Endoscope Reprocessing

Lisa Maragakis, MD, MPH

HICPAC Member

Co-Chair, HICPAC Endoscope Workgroup

Dr. Maragakis provided an update on the HICPAC Endoscope Workgroup's goal and charge as well as progress on drafting and revising an Essential Elements document. Endoscopes are high-risk medical devices. There have been outbreaks of bacterial infection associated with these devices, sometimes attributed to improperly reprocessed endoscopes related to the elevator design feature found on some endoscopes such as a duodenoscopes. Endoscope reprocessing is a highly complex and technical procedure with many potential risks for error.

At the November 2015 HICPAC meeting, HICPAC member Vickie Brown presented a summary of the current challenges that institutions on the front lines face when they try to implement and oversee endoscope reprocessing programs in a comprehensive, safe way that mitigates the associated risks for patients. As a result of that presentation and other discussions, HICPAC formed the Endoscopy Reprocessing Workgroup. The group's initial meetings focused on refining its goal and charge.

Goal

- To help healthcare facilities identify the key elements needed for a reliable, high quality system for endoscope reprocessing which minimizes infection risks.

Workgroup Charge

- To identify the elements that are necessary to achieve this goal, including risk assessment tools; training and competency assessments; measurement; and management of the endoscope reprocessing infrastructure.
- To deliver these draft elements/recommendations to HICPAC for deliberation and input in order to produce recommendations from HICPAC to CDC.

The workgroup is broadly inclusive of partners from the federal government, professional societies, CDC, HICPAC, and other relevant organizations. Because many groups have already done work in this area, an important goal is to avoid duplication of efforts and to generate a value-added set of recommendations and documents that will help facilities.

The group first convened in the fall of 2015 and has held biweekly conference calls since. They refined their goal, charge and scope and have delineated areas that are beyond their scope. The group's goal is to provide assistance to institutions that have endoscope reprocessing programs so that they have the appropriate elements in place to ensure patient safety. The group also identified gaps and priorities among the various activities associated with endoscope reprocessing. Their recent conversations have focused on drafting and revising an Essential Elements document, which had been submitted to HICPAC members and liaison members for their review and input.

The Essential Elements document is divided into the following categories:

Administrative: What does an institution need to have in place to have appropriate administration of an endoscope reprocessing program?

Accountable Leadership

- Resources and infrastructure should be available so that endoscope reprocessing can happen in a safe and comprehensive way.
- Leaders should be designated and given authority to oversee the program and oversee required changes

Policies

- Created with multidisciplinary input
- Address the selection, use, transport, reprocessing, storage of endoscopes in compliance with manufacturer instructions for use; training and competency assessment for all staff involved in the program; documentation that occurs during reprocessing; and quality assurance methods
- Consistent with all regulatory requirements, accrediting organizations, and standards and recommendations from professional organizations

Management

- Ensure that single-use devices are not reprocessed
- Ensure that occupational health protections for the workers who reprocess these devices are addressed, including their personal protective equipment (PPE), chemicals that are used, and other considerations
- Ensure that scheduling, staffing, and on-hand inventory allows adequate time for reprocessing
- Provide specific access to infection prevention knowledge and expertise

- Ensure adequate, ongoing training, education, and certification for all involved staff
- Ensure that water quality meets standards
- Ensure that appropriate documentation is kept at every stage of the reprocessing

Documentation

- Requirements may vary depending upon which endoscopes are being used, the method of reprocessing, the type of germicide, and other factors
- Endoscope and patient identifiers must be documented for traceability
- Times and dates for each step of the process should be included, including the pre-cleaning step, which incorporates point-of-use cleaning by those using the endoscopes and includes appropriate flushing of channels and appropriate cleaning so that the device does not sit for a long period of time before it is transferred to the reprocessing team
- Fluid tests of efficacy, appropriate concentrations, expiration dates
- Preventive maintenance and repair of devices, as lapses in maintenance play into risk
- Retain documentation of endoscopes, even those that are retired, as well as maintenance and repair of AERs, sterilizers, or other equipment

Inventory

- Identify all endoscopes by:
 - Make
 - Model
 - Location of use
 - Manufacturer instructions for use and reprocessing
 - Reprocessing equipment and personnel that are responsible for the device
 - Condition: this work is challenging because facilities are likely to use scopes in a wide range of outpatient and inpatient locations
- Ensure that each scope has a unique identifier for tracking

Physical Setting

- Separate, dedicated space for endoscope reprocessing
- One-way workflow that separates clean from dirty spaces
- If a separate room is used for manual cleaning, negative airflow should be present in that space
- Ensure proper ventilation, humidity, temperature
- Provide a clean hand washing sink with eyewash in addition to, and separate from, the reprocessing sink(s)
- Two sinks or a divided sink for washing and rinsing endoscopes
- Ensure that manufacturer instructions for use for endoscopes, AERs, and chemicals are available on site and that staff responsible for reprocessing the devices know where the instructions are and can easily access them

Training and Competencies

- Include the rationale for the reprocessing steps in training for front-line workers. The system will be more robust when the staff know why they are completing each of the steps, and there will be a better chance that they will recognize lapses
- Model-specific training and competency assessment based upon manufacturer instructions for use and equipment used

- Address the reprocessing of other reusable accessories that also break the mucosal barrier, such as biopsy forceps and other accessories that will be used with the endoscope
- Ensure that trainers and supervisors are also competent to reprocess endoscopes in order to train and assess the front line staff
- Assessment of staff competency:
 - Should be conducted upon hire and at least annually
 - Reassessment should occur when new equipment or chemicals are purchased and used and whenever manufacturer instructions for use change
 - Should include direct observation of reprocessing as well as paper-based competency assessment
 - Should include all steps of the process, from pre-cleaning to storage
 - Should include a review of manual reprocessing
 - Should include training on performing rapid verification tests when used by the facility

Quality Assurance (QA)

- Comprehensive gap analysis should occur, including all components, processes and equipment
- Periodic audits of documentation and observations of reprocessing should take place to identify risks and errors
- Risk assessment of any new supplemental measures should occur specific to the institution, equipment that is used, and other factors to determine which measures will be implemented
- Risk assessment should be conducted when the manufacturer instructions for use allow for intermediate reprocessing and use of a sheath to understand how best to utilize the sheath
- Gap analysis and risk assessment should be repeated periodically and when new equipment is purchased, manufacturer instructions for use change, or new recommendations and guidance are issued

The workgroup also discussed several other issues that they opted not to incorporate into the Essential Elements document, but to place in the “parking lot.” These topics are important but outside the scope of this document.

- Pre-market clearance processes
- Post-market regulatory activities
- Surveillance for post-procedure infections and MDROs
- Identification and reporting procedures for breaches in endoscope reprocessing protocols

The workgroup asked for HICPAC’s input on its work to date:

- Are there any additional considerations or feedback on the Endoscope Reprocessing Workgroup’s scope and charge?
- Is the Essential Elements document missing any important points?
- How much detail should the document include on the reprocessing process (i.e., should essential reprocessing steps [e.g., pre-cleaning, leak testing, manual cleaning with

brushes, quality monitoring of the disinfectant, scope storage principles] be included as a section of the document)?

- Are there elements in the document that require further elaboration?
- Should this document include some discussion of supplemental measures that endoscopy units can consider (e.g., microbial culturing, monitoring of manual cleaning using adenosine triphosphate (ATP) or other tests, repeat high-level disinfection (HLD))? If so, how should this be done (e.g., table of pros/cons)?
- Are there areas the document should highlight where additional research/ data is needed?

Discussion Points

HICPAC commented that the Essential Elements could apply to other devices, such as probes, that are also reprocessed. The workgroup discussed whether the focus should only be on duodenoscopes, scopes with elevators, all scopes, or other devices as well. The workgroup decided to focus on all channeled scopes at this point. The guidance is analogous to other devices, but there are implications to broadening its scope, which might not serve to move issues forward.

There was support among HICPAC for the structure of the Essential Elements document and its focus on key points. Some specific elements of the cleaning and disinfection process could be included. For instance, the document might highlight the importance of pre-cleaning, leak testing, and brush cleaning. Including discussion about supplemental strategies could imply endorsement of these practices but including a brief description of these supplemental practices in a table of “issues to consider” might be an option.

CSTE noted that additional detail regarding the essential reprocessing steps would be important to include. In terms of operationalization, it may be helpful to include a sample policy or example to illustrate the expected level of detail in a program. Smaller facilities may not have experienced infection preventionists, and an example could provide them with guidance in creating their own policies. Examples of risk assessments and gap analyses would also be helpful.

HICPAC suggested that including guidance regarding the management of a breach or problem in the Essential Elements document or a supplement could be useful. Local epidemiologists and infection preventionists may be insecure in this area. A thought process or algorithm of areas to consider, whom to contact, etc. would be helpful..

There was a question regarding facilities that outsource reprocessing and how to handle those responsibilities and arrangements.

The workgroup also discussed the available level of expertise outside acute care facilities. Most complicated procedures occur in hospitals, but an increasing amount of endoscopy is performed in ambulatory care facilities, outpatient surgical facilities, and the like. There was concern regarding whether the expertise to follow these detailed guidelines is available in these settings. While there are requirements for facilities to have an infection control presence, access to individuals with infection control and reprocessing expertise can be limited. Outside resources may be available in communities, such as through a local Association of Professionals of Infection Control and Epidemiology (APIC) chapter or other sources. The guidelines should take into account how a less-well-staffed, ambulatory facility in which one person may have many responsibilities can meet these requirements.

The workgroup also discussed how to incorporate the concept of certification without endorsing a specific certification or education opportunity.

HICPAC commented that certain infrastructure elements in the reprocessing environment can improve and sustain reprocessing reliability. The manufacturing sector and related sectors, for instance, post standard work steps, visual guidance, or video clips of procedures. HICPAC might make a statement about best practices in this area or highlight this area for further research.

Regarding dissemination and implementation of the guidance, CSTE observed that there would be value in ensuring that accrediting agencies and organizations are fully aware of the final document and can see them as part of their education efforts. The document could also serve as the basis for a checklist for implementation.

The VA cautioned that it should not be assumed that infection control staff know how to implement these guidelines. They understand the principles of the guidance but not necessarily the complexities of the work. Trying to “do the same thing all the time, every time” in this environment is challenging. There should be a Standard Operating Procedure (SOP) that can be posted in the area. An SOP has the advantage, especially in smaller places, of being available to support personnel who are trained in a process but who may not perform it every day. .

Many groups have done work on this issue. HICPAC discussed integrating the various groups’ products into this document. The workgroup representatives from professional societies were willing to share their work during the calls. A packet could be assembled of existing checklists, assessment surveys and other tools that facilities can adapt.

The Joint Commission agreed that it is important to consider human factors. In its courses on endoscope cleaning, the Joint Commission discusses human factors and SOPs. There is significant turnover in staff that perform the cleaning, making it all the more important to have SOPs and attention to human factors to avoid failures.

APIC concurred that infection preventionists are not necessarily experts in the actual processes of cleaning scopes. An SOP is critical. Infection preventionists may learn the steps from the individuals who do the work. With that in mind, the principles of infection prevention can be essential for responding to breaches. Infection preventionists should be well-versed in endoscope reprocessing but they should also make use of partnerships with the individuals who do the reprocessing work.

HICPAC noted that the brevity of the document makes it more useful. A toolkit could be developed around the document to provide examples of SOPs, management, or other relevant guidelines.

Dr. Bell asked whether the document can address the variability in automatic device reprocessors and equipment that all have different SOPs, and whether the document could suggest uniformity whenever possible. Such a statement would be helpful, but it may not be realistic, given the expense of the equipment and the investments that have already been made. The document can allude to the idea as an ideal as facilities make choices about equipment. The concept is important and a potential area for future research and work.

SCCM noted that the cleaning and reprocessing process is dictated by the manufacturer. In the event of a failure even when an organization follows all of the steps and audits full compliance, the document could offer recommendations for a process thereafter to inform the manufacturer and FDA that there is a problem with the stated reprocessing process.

Dr. Maragakis said that the workgroup will consider including that idea as well as the breach notification.

Devices in Healthcare Settings: Design Considerations for Infection Control

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Dr. Michael Bell said that in pursuing patient safety and infection prevention, groups that are normally targeted to receive information may not be the appropriate audience. For instance, staff in materials management, reprocessing, and environmental services play a crucial role in maintaining safety of devices. Further, the purchasing department has control over which devices are in the hospital. As a field, infection prevention may need to work more closely with purchasing departments.

A hospital that he recently visited has a system in which the environmental services lead and the materials management lead both have the authority to request different brands of devices if a certain brand is too difficult to clean or has other challenges. That empowerment and connection between the people who manage the materials and the people who are charged with purchasing the materials represents a critical innovation. Non-clinicians can be armed with guidance to help them make decisions.

Issues to consider for devices that require reprocessing include:

Cleanability

- Processes indicate that the devices must be cleaned, but it should be recognized that the device surface textures, seams, materials, and design elements may make it all but impossible to clean them effectively and consistently.

Assessability

- Is it easy to tell if the reprocessing was successful? Can colors and contrast be used more effectively to help users determine whether a device is clean or not? There may be new ways to utilize molecular indicators, color changes, or other approaches. Individuals doing this work on a daily basis experience high turnover and are likely to have a limited background in microbiology. If possible, it would be helpful to have clear indicators for them.

Similarity

- In general, the processes could be more consistent and the tools more familiar.

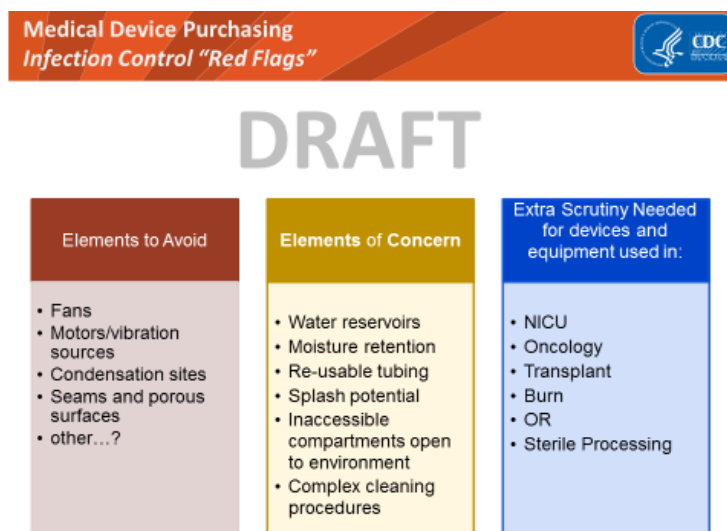
Issues to consider for equipment used in high-risk locations, based on where they are used as well as who might be exposed, include:

- Air current generation: devices that blow air should probably not be situated in high-risk locations
- Moisture retention or reservoirs: devices that use water will likely have NTMs, mold, and opportunistic pathogens that should be avoided

These categories can be useful for delivering this information to individuals who are not specialists in infectious disease, but who implement the actions. Other issues for consideration include:

- Porosity of surfaces and materials: for instance, foam insulation panels are not cleanable. Wooden surfaces should not be in ORs. Garments should not hang on the back of the door in a procedure room.
- Promoting innovative options, such as fanless cooling; retardant treatments to prevent the adhesion or formation of biofilms, such as are used in the shipping industry; microbicidal/static characteristics of equipment; and self-cleaning nano-coatings

Several draft documents are in development to describe “elements to avoid” in purchasing medical equipment, “elements of concern” that can guide purchasing and to stimulate innovation in industry, and high-risk locations to specify the zone of care that requires special treatment regarding medical devices.



Discussion Points

Dr. Shannon Keckler added that CDC has approached this idea from a “bug-centric” point of view, focusing on HAIs and the ecology of how the microbes work. They welcome as much assistance as possible regarding this large topic area.

While it is important to articulate the factors that are important to assess, HICPAC expressed concern about placing the onus of responsibility to assess these factors on the purchasers, who are often reacting to specific requests from other groups within a hospital. It is a lot to ask them to assess products and compare them to others that are available. Further, purchasers are often bound by contractual agreements and may not necessarily have access to a full range of

products. HICPAC hoped that FDA could incorporate some of these concepts into the device review process.

HICPAC supported the idea of extra scrutiny in high-risk areas; however, at this point, high-risk patients are housed throughout a facility. It may not be beneficial to bring specific attention only to certain areas, as devices are used in many places.

There was support for issuing this guidance to motivate device manufacturers to invest effort into device redesigns that eliminate these problems. Purchasers are an appropriate pressure point. Purchasers could use explicit advice or a checklist from infection control regarding factors that should affect purchasing decisions. There may be issues regarding contracts, but if purchasers have power to choose equipment based on infection control criteria, then manufacturers may have the necessary incentive to fix the problems.

There are limitations to the success of this strategy, many of them associated with the purchasing process and by the ability and role of a purchaser to stand up for these concepts. If there are not alternatives to equipment, then facilities may be “stuck” with what is available, even if it is high-risk. The people who are trying to make these points at any level would find supportive documentation useful. Infection preventionists also find issues that arise because a piece of equipment did not need an infection prevention review. Information about medical device “red flags” could be distributed throughout an organization, including the supply chain and purchasing department, to provide a helpful structure.

AORN said that while the document is strong, it may not be practical to implement with purchasers. The document may need to be shared with manufacturers. There is a great deal of equipment in the OR, and nearly every piece of equipment has a fan to cool it. If alternative products are not available, then facilities may be caught in the middle. Pressure on manufacturers can be helpful, but it can still take years to arrive at solutions.

APIC supported articulating the “why” behind the elements to avoid, with data and elements of substance. Value analysis groups respond to robust information, and there are competing priorities for individuals who may want certain products.

IDSA said that there is no single, perfect strategy, but found this idea appealing. Purchasing decisions should come through a common pathway or gateway. Many institutions require construction projects to be reviewed by Infection Control but do not require similar review of equipment. The sensitivity and specificity may be adjusted according to the resources and priorities of the organization. This draft document is a strong starting point to set the standard that equipment should not be purchased by a hospital without presuming that it could cause infection.

Dr. Keckler asked about the usefulness of a tiered approach, with a basic level, a deeper level for the providers who want it, and an even-deeper level for manufacturers.

HICPAC said that the question is not whether steps should be taken in this direction, but rather how to take steps that will be most effective. Rather than a deeper approach, a more summative product might be helpful. If a purchaser is looking at two devices, each with “red flags,” he or she will need a tool to determine which to choose. Such a tool could rate devices on a scale of one to five stars, for instance. The Centers for Medicare and Medicaid Services (CMS) is

moving toward a star rating for all hospital quality. A similar approach could be utilized in this instance and serve as an effective communication strategy.

Additional benefit from this work could be additional pressure on the competitive marketplace for making medical devices. Simple changes could be instituted to remove the possibility of human error as people work with these complicated devices and equipment under a great deal of pressure. This information will illustrate the problems that hospitals and healthcare have identified and drive manufacturers to engineer out potential errors.

Dr. Bell thanked HICPAC for the helpful comments and input, noting that it will be more difficult to move quickly in some areas, while some areas may be amenable to prompt change.

Update on Pre-Market Notification Requirements Concerning Gowns Intended for Use in Healthcare

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Mr. Terrell Cunningham briefed HICPAC on the current status of FDA's review and regulation of surgical/isolation Gowns. These gowns are one of the primary product lines for which his branch is responsible.

FDA has enacted several key efforts regarding the regulation of surgical gowns, including the following:

- A draft guidance was published in June 2015
- The final guidance was published on December 8, 2015
- As a follow-up to allow for interaction with industry, a Webinar on the guidance was held on January 21, 2016 with approximately 200 attendees
- FDA will participate in the Association for the Advancement of Medical Instrumentation (AAMI)-Protective Barrier and American Society for Testing and Materials (ASTM) F23.40 Joint Meeting on April 19, 2016 in Bethesda, Maryland; this meeting represents an unusual opportunity to devote an entire day to one product line and is convened in response to the need to consider the status of gowns and to hold discussions with industry
- A Joint CDC/FDA Gown Workshop is proposed and will depend on the outcome of the AAMI/ASTM meeting
- The primary output of this collaboration will be an update of the 1993 Gown Guidance Document

Several factors affect FDA and its partners' work with surgical gowns. The 1993 document is quite old. In 2000, FDA down-classified isolation gowns from a Class II device to a Class I exempt product. In 2003, an AAMI PB70 document was established and published. It was recognized by FDA in 2004. In January 2015, the National Institute of Occupational Safety and Health (NIOSH) released results of a study of isolation gowns used in healthcare settings that